



# Significance of Secreted Frizzled Related Protein 4 (SFRP4) in Type 2 Diabetic and non Diabetic Subjects in the Rural Agricultural Population Who are Exposed to Pesticides for the Prediction of Diabetes Mellitus

Velayutharaj A.<sup>1</sup>, Muthumani L.<sup>2</sup>, Senthilnathan R.<sup>3</sup>, Rajendran S.M.<sup>4</sup>, Shivakumar R.<sup>5</sup>, Saraswathi R.<sup>6</sup>

<sup>1</sup>Assistant Professor of Biochemistry, Trichy SRM Medical College Hospital & Research Centre, Tiruchirapalli, Tamilnadu, India; <sup>2</sup>Assistant Professor of Medicine, KAPV Government Medical College Hospital, Tiruchirapalli, Tamilnadu, India; <sup>3</sup>Associate Professor, Department of Oro-Maxillary Facial Surgery, Balaji Medical College Hospital, Chennai, Tamilnadu; <sup>4</sup>Former Professor & HOD of Medicine, Stanley Medical College Hospital, Chennai, Tamilnadu, India; <sup>5</sup>Professor of Pharmacology, SRM Dental College Hospital, Chennai, Tamilnadu, India; <sup>6</sup>Assistant Professor of Microbiology, Trichy SRM Medical College Hospital & Research Centre, Tiruchirapalli, Tamilnadu, India.

## ABSTRACT

**Introduction:** Diabetes mellitus and its complications have become a major health problem for the public of South East Asians especially in India. Exposure to organophosphorus pesticides which are very much in use for the agriculture purpose worldwide produces disorders of glucose homeostasis, because there is increasing evidence of environmental pollutants especially pesticides to the development of insulin resistance and type2 diabetes mellitus.

**Background:** To study the significance of Secreted Frizzled Related Protein4 (SFRP4) levels in both diabetic and non diabetic rural agriculture population who are exposed to pesticides for the prediction of diabetes mellitus. Total 46 Type 2 Diabetic patients & 42 non diabetic subjects were included in this study.

**Results:** The Pearson correlation coefficient was used to find the correlation between SFRP4 and Glycated hemoglobin (HbA1c) & Fasting glucose. And the correlation was found between SFRP4 levels with HbA1c ( $R=0.65$ ) and also found between SFRP4 and fasting glucose levels ( $R=0.54$ ) and both are statistically significant ( $p<0.05$ ).

**Conclusion:** If properly intervene the population with proper health education regarding precautionary measures for the use of pesticides and awareness of diabetes who have a strong family history of diabetes mellitus with upper normal level after testing this new marker SFRP4, we can delay or even may reduce the incidence of diabetes mellitus in the rural population due to the exposure of pesticides.

**Key Words:** SFRP4-Secreted Frizzled Related Protein, HbA1c-Glycated Hemoglobin, T2DM-Type 2 Diabetes Mellitus, OPC-Organophosphorus compounds.

## INTRODUCTION

With all precautionary and therapeutic approaches by the Government and Non-governmental organizations diabetes and its complications have become a major health problem

for the public of South East Asians especially in India. There are many risk factors have been identified like lifestyle factors, genetic factors and for the prediction of diabetes that have been proposed and tested. Apart from these lifestyles and genetic factors, pesticides like organophosphorus com-

### Corresponding Author:

Dr. L. Muthumani, Assistant Professor of Medicine, KAPV Government Medical College Hospital, Tiruchirapalli, Tamilnadu, India;  
E-mail: drmuthumani@yahoo.co.in

ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 23.02.2018

Revised: 04.03.2018

Accepted: 14.03.2018

pounds (OPCs) which are very much in use for the agriculture purpose worldwide, disorders of glucose homeostasis are one of the most important complications following exposure to organophosphorus pesticides, because there is increasing evidence of environmental pollutants especially pesticides to the development of insulin resistance and type 2 diabetes mellitus<sup>1</sup>. *Hectors et al.* stated that beta cell function has been found to be disrupted by the organophosphate pesticides like malathion and disturbance in carbohydrate metabolism<sup>2</sup>. Many previous studies have proved that the use of OPCs like malathion, diazinon, chlorpyrifos, dichlorvos without any proper precautionary measures may cause different health problems, including endocrine, reproductive, nervous, and immune systems<sup>3, 4, 5</sup>.

An adipocytokine known as Secreted frizzled related protein 4 (SFRP4) one of the recently discovered group of 5 proteins has been described as a potential bio marker of early pancreatic beta cell dysfunction<sup>6</sup>. And it was stated in a study that there was a significant inverse correlation of SFRP4 expression in human pancreatic islets with insulin secretion and positive relationship with HbA1C levels was observed<sup>7</sup>. There was much focus on the risk factors for diabetes has been elaborated on the basis of life styles and genetics. So the aim of the study is to know the relationship between SFRP4 levels and type-2 diabetes mellitus among pesticide users in the rural population.

**Aim:** To study the significance of *SFRP4* levels in both diabetic and non diabetic rural agriculture population who are exposed to pesticides for the prediction of diabetes mellitus.

### Objectives

1. To know the levels of *SFRP4* in Diabetes and non-diabetes persons.
2. To reveal the role of pesticides in relation to the *SFRP4* levels in Diabetes and non-diabetes persons.

### MATERIALS AND METHODS

- 46 Type 2 Diabetic (T2DM) & 42 non diabetic Male and Female subjects with age ranges from 20 to 75 were included in this study.
- Inclusion criteria: The study subjects who were exposed to pesticides for more than one year living in the rural area near by the Tertiary Care Teaching Hospital
- Exclusion criteria: Type-1 Diabetes Mellitus (DM), Secondary causes of DM, Gestational DM and Diabetic patients with its complications were excluded from this study
- After got the informed written consent from all patients and subjects, 5 ml of fasting blood sample was collected, 3ml in a clot activator tube for the analysis of Fasting plasma glucose in BS 420 auto analyzer, serum quantitative analysis of *SFRP4* by ELISA method

in the Biorad-680 system and 2 ml of blood into the EDTA tube for the analysis of HbA1c% by NGSP/IFCC approved method.

### RESULTS

The results were analyzed in SPSS16.0 version. The Mean value of *SFRP4* among diabetic study subject was  $3.2 \pm 0.6$  (Normal value considered was  $<3$ ) and for the non diabetic people  $2.3 \pm 0.5$  and the difference is statistically significant ( $p < 0.05$ ). The Pearson correlation coefficient was used to find the correlation between *SFRP4* and HbA1c & Fasting glucose. And the correlation was found between *SFRP4* levels with HbA1c ( $R=0.65$ ) and also found between *SFRP4* and fasting glucose levels ( $R=0.54$ ) and both are statistically significant ( $p < 0.05$ ).

**Table 1. Comparison of the values of Secreted Frizzled Related Protein 4 (*SFRP4*) in Diabetic and Non diabetic study groups**

Study Subjects	SFRP4 values		p-value
	Mean	SD	
Diabetic group	3.2	0.6	<0.05
Non Diabetic group	2.3	0.5	

### DISCUSSION

Since T2DM is a progressive disease which does not cause specific symptoms for many years, diagnosis at an early stage is of utmost importance and to reduce the burden for our health system in general. In spite of many biomarkers available to confirm the disease, the recent trend is to control the disease by the target base inhibiting of enzymes or proteins. The Malekirad <sup>et al</sup> study had confirmed that farmers are prone to neuropsychological disorders and diabetes caused by organophosphorous compounds (OPC) exposure<sup>8</sup>. Suarez-Lopez JR, Lee DH, Porta M, et al. stated those after decades of exposure to PCBs and OCPs at background environmental levels, glucose homeostasis may worsen irrespective of their BMI after 5<sup>th</sup> decade of life<sup>9</sup>. Hansen et al. found that there was an increase in the prevalence of prediabetes among the Bolivian pesticide sprayers compared with a control group<sup>10</sup>.

Michael et al in their prospective study showed that higher *SFRP4* concentrations are associated with T2DM and the metabolic syndrome and *SFRP4* concentrations are a novel marker of impaired glucose and triglyceride metabolism which is consistent with our study<sup>11</sup>. Elevated systemic *SFRP4* causes reduced glucose tolerance through decreased islet expression of  $Ca^{2+}$  channels and suppressed insulin exocytosis thus *SFRP4* provides a link between islet inflammation and impaired insulin secretion<sup>12</sup>.

Mahdi and his colleagues pointed out that increased *SFRP4* causes reduced glucose tolerance through decreased islet expression of  $\text{Ca}^{++}$  channels and suppressed insulin exocytosis thus provides a link between islet inflammation and impaired insulin secretion. Further, they have suggested that *SFRP4* could be a potential biomarker for islet dysfunction in T2DM. The elevation of *SFRP4* in serum several years before the diagnosis highlights this protein as a potential biomarker for the low-grade islet inflammation that is commonly seen in T2D, and it might prove useful for early disease detection in combination with glucose and other biomarkers and their data also raised the exciting possibility that *SFRP4* could be a therapeutic target for specific treatment of islet dysfunction<sup>13</sup>. Also in a study by the Shazia Anwer Bukhari found that there is a possible treatment of type 2 diabetes mellitus by inhibiting the protein SFRP4 using the compounds like cyclothiazide, clopamide and perindopril<sup>14</sup>. Brix JM<sup>etal</sup> demonstrated that increased levels of *SFRP4* found in patients with different types of diabetes, suggesting that *SFRP4* irrespective of type of diabetes is generally involved in islet dysfunction and potentially due to subclinical inflammation<sup>15</sup>. In our study also the findings showed that there is a statistically significant association between *SFRP4* levels and Type-2 Diabetes mellitus.

## CONCLUSION

Since diabetes now considered as one of the global economical burden because of its complications, it is mandatory to find out newer markers and therapeutic approach. Many previous studies had been pointed out that *SFRP4* is a potential marker of beta cell dysfunction. So if properly intervene the population with proper education regarding precautionary measures for the use of pesticides and awareness of diabetes who have a strong family history of diabetes mellitus with upper normal level after testing this new marker *SFRP4*, we can delay or even may reduce the incidence of diabetes mellitus in the rural population due to the exposure of insecticides. Further large scale population study is needed for the importance of *SFRP4* estimation in T2DM in farmers who are in the exposure of OPCs for the newer therapeutic implications.

**Conflict of Interest:** Authors have no conflict of interest

## ACKNOWLEDGEMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors /

editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

## REFERENCES

- Swaminathan K . Pesticides and human diabetes: a link worth exploring? 2013. Diabet Med.30(11):1268-71.
- Hectors TL<sup>1</sup>, Vanparys C, van der Ven K, Martens GA, Jorens PG, Van Gaal LF, Covaci A, De Coen W, Blust R. Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. Diabetologia. 2011 Jun;54(6):1273-90. Epub 2011 Mar 27. [PubMed]
- Soltaninejad K, Abdollahi M. Current opinion on the science of organophosphate pesticides and toxic stress: A systematic review. Med Sci Monit 2009;15:75-90.
- Mostafalou S, Abdollahi M. Current concerns on genotoxicity of pesticides. Int J Pharmacol 2012;8:473-4.
- Mostafalou S, Abdollahi M. Concerns of environmental persistence of pesticides and human chronic diseases. Clin Exp Pharmacol 2012;S5:e002.
- K. Bergmann, G. Sypniewska Secreted frizzled-related protein 4 (SFRP4) and fractalkine (CX3CL1) — Potential new biomarkers for  $\beta$ -cell dysfunction and diabetes. Clinical Biochemistry 47 (2014) 529–532.
- Grazyna Sypniewska . How to diagnose diabetes? Biochemia medica 2014;24(Suppl 1) S31-34.
- Malekirad AA et al. Neurocognitive, Mental, and Glucose Disorders in Op-Exposed Farmers Arh Hig Rada Toksikol 2013;64:
- Suarez-Lopez JR, Lee DH, Porta M, Steffes MW, Jacobs DR Jr. Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up 2015. Environ Res. 137:485-94.
- Hansen MR, Jørs E, Lander F, Condarco G, Schlünssen V. Is cumulated pyrethroid exposure associated with prediabetes? A cross-sectional study. J Agromedicine. 2014;19(4):417-26.
- Michael M Hoffmann, Christian Werner, Michael Böhm, Ulrich Laufs and Karl Winkler. Association of secreted frizzled-related protein 4 (SFRP4) with type 2 diabetes in patients with stable coronary artery disease. Cardiovasc Diabetol. 2014; 13: 155.
- Wilson C. Diabetes: SFRP4—a biomarker for islet dysfunction? Nature Reviews Endocrinology 2013; 9, 65.
- Mahdi T, Hänzelmann S, Salehi A, Muhammed SJ, Reinbothe TM, Tang Y, Axelsson AS, Zhou Y, Jing X, Almgren P, Krus U, Taneera J, Blom AM, Lyssenko V, Esguerra JL, Hansson O, Eliasson L, Derry J, Zhang E, Wollheim CB, Groop L, Renström E, Rosengren AH. Secreted frizzled-related protein 4 reduces insulin secretion and is overexpressed in type 2 diabetes. Cell Metab. 2012 Nov 7;16(5):625-33.
- Shazia Anwer Bukhari , Waseem Akhtar Shamshari , Mahmood-Ur-Rahman , Muhammad Zia-Ul-Haq, and Hawa Z. E. Jaafar. Computer Aided Screening of Secreted Frizzled-Related Protein 4 (SFRP4): A Potential Control for Diabetes Mellitus. Molecules 2014, 19, 10129-10136.
- Brix JM, Krzizek EC, Hoebaus C, Ludvik B, Scherthaner G, Scherthaner GH Secreted Frizzled-Related Protein 4 (SFRP4) is Elevated in Patients with Diabetes Mellitus. Horm Metab Res. 2016 May;48(5):345-8.